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PROSPECTIVE PROCESS VALIDATION FOR POLYHERBAL ORAL LIQUID PREPARATION

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ABSTRACT

Background: Process validation is an enduring progression indicating regulation of all aspects of the process. Pharmaceutical validation and process control are necessary to make sure that the drug product will congregate the specified standards for identity, quality, purity, safety and efficacy. **Objective:** Present work was carried out to validate the manufacturing procedure of oral liquid formulation and to provide assurance that it meets with predetermined specifications. **Materials and Methods:** In this prospective process validation, critical process parameters were identified, the protocol and report were made and results of critical parameters were checked for three consecutive batches to assure reproducibility of the results. **Results:** The identified critical process parameters were checked for their compliance and also for their reproducibility. The filling and sealing quality were also determined for each batch. **Conclusion:** The manufacturing process of polyherbal Entoban syrup was found to be reproducible for three batches and all parameters were complying with the specifications and validated as per the guidelines mentioned in prospective process validation.

KEYWORDS: Process validation, Polyherbal formulation, Critical process parameters, Specifications.

INTRODUCTON

Validation is an imperative component of quality assurance; involving an organized evaluation of systems, facilities and processes aimed at determining whether they perform their intended functions adequately and consistently as specified. The concept of validation was first proposed by two Food and Drug Administration (FDA) officials, Ted Byers and

Bud Loftus, in the mid 1970's in order to improve the quality of pharmaceuticals.[1] A validated process is one which has been demonstrated to provide a high degree of assurance that uniform batches will be produced meeting the required specifications. Validation in itself does not improve processes but confirms that the processes have been appropriately developed and are under control.[2] Adequate validation decreases the risk of defect costs, the risk of regulatory noncompliance and requires less in-process controls and end product testing.

Process validation is the means of ensuring and providing documentary evidence that processes (within their specified design parameters) are capable of repeatedly and reliably producing a finished product of the required quality.[3] The U.S Food and Drug Administration (FDA) guidelines state that the process validation is the established documented evidence which provides a high degree of assurance regarding that specific process.[4] The first edition of the Orange Guide the British version of GMPs, which was published in 1971 contains a section titled "Verification of Procedures" that states, "Procedures should undergo a regular critical appraisal to ensure that they remain capable of achieving the results which they are intended to achieve". This term now here appeared in the U.S.F.D.A. documentation in the compliance programme entitled "Drug Process Inspections" issued in June 1978 (before publication of the revised cGMP Regulations).[5]

Process validation establishes the flexibility and constraints in the manufacturing process for the attainment of desirable attributes in the drug product while preventing undesirable properties. It would normally be expected that process validation be completed prior to the release of the finished product for sale (prospective validation).[6] Process validation of any formulation is carried out in three stages: First stage is process design stage. The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities. Second stage is process qualification stage during which, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing. Third stage is continued process verification stage. Ongoing assurance is gained during routine production that the process remains in a state of control.[7]

At various stages in a validation exercise there are needs for protocols, documentation, procedures, specifications and acceptance criteria for test results.[8] All these need to be reviewed, checked and authorized. Before process validation can be started, manufacturing equipment and control instruments as well as the formulation must be qualified. The

information on a pharmaceutical product should be studied in detail and qualified at the development stage, i.e., before an application for marketing authorization is submitted. This involves studies on the compatibility of active ingredients and excipients, and of final drug product and packaging materials, stability studies, etc. Other aspects of manufacturing must be validated including critical services and supporting operations such as equipment cleaning and sanitation of premises. Proper training and motivation of personnel are prerequisites to successful validation.[2] Manufacturing process of liquid syrup involves many steps in production operations starting from raw material procurement then its analytical testing for purity and strength to packaging of finished product and it's testing for assays. With this background the present work was carried out to validate the manufacturing procedure of oral liquid syrup formulation and to provide assurance that it meets with predetermined specifications.

MATERIALS AND METHODS

The raw materials were tested for its quality control parameters. Individual certificate of analysis was generated and it was assured that all the materials are complying with in-house specifications of the industry.

Critical quality attributes

Based on the pilot batches studies, following parameters were identified as critical quality attributes which have impact on finished product quality.

- The quality of purified water used in manufacturing of syrup.
- Stirrer speed at which the liquid mixture is stirred throughout the process.
- pH, viscosity and density of final product.
- Description and taste of the final product.
- The filled volume of final product which is delivered with filling nozzle.
- Sealing quality of the packed bottle.

Three batches were checked for above mentioned parameters and finally validation protocol and report were generated. Viscosity was measured with Brookfield viscometer. Conductivity of the purified water was measured conductivity meter.

Preparation syrup Entoban

Herbs were purified and extracted in an extractor filled with deionized water. After extraction, filtering of said aqueous extract was done through cotton cloth. The filtrate was transferred to the evaporator. The filtrate was concentrated by rotary evaporator to give thin layer of thick syrup residue extract. Manufacturing preparation tank was filled with deionized water and allowed to reflux for 10 to 15 minutes. (Solution 1) When boiling started then sucrose was added slowly with constant stirring and then heated for 30 minutes to obtain the homogenate syrup. Desired flavor was added and mixed the contents vigorously (in solution 1).

In a separate tank methylparaben, propylparaben, propylene glycol, glycerol and citric acid was dissolved in deionized water. Heated slowly with stirring constantly so that it was properly mixed, the solution was filtered and mixed with a solution 1. It was done with continued stirring (solution 2) for another 10 minutes. Deionized water was taken in the jacketed kettle and the two solutions were added in it (solution 1 + solution 2). Additional heating and stirring the mixture was done to obtained syrup. The cooling water circulation was started so that the syrup was allowed to cool to room temperature. The resulting syrup was transferred in storage tank.

Sampling for process validation

Initially, 30 ml of purified water sample was taken and tested for its appearance, pH and conductivity. Finally 30 ml of syrup sample was taken which was kept in storage vessel after filtration and then tested for critical process parameters mentioned in process validation protocol. The samples were collected in amber colored pet bottles.

RESULTS AND DISCUSSION

The concept of validation has expanded through the years to embrace a wide range of activities from analytical methods used for the quality control of drug substances and drug products to computerized systems for clinical trials, labeling or process control.[9] To further enhance the effectiveness and safety of the drug product after approval, the United States Food and Drug Administration (FDA) require that the drug product be tested for its identity, strength, quality, purity and stability before it can be released for use.[10] For this reason, pharmaceutical validation and process controls are important in spite of the problems that may be encountered.[6] Process controls include raw materials inspection, in-process controls and targets for final product. The purpose is to monitor the on-line and off-line performance

of the manufacturing process and then validate it. Even after the manufacturing process is validated, current good manufacturing practice also requires that a well-written procedure for process controls is established to monitor its performance.[11] Process validation is a requirement of current Good Manufacturing Practices (GMPs) for finished pharmaceuticals (21CFR 211) and of the GMP regulations for medical devices (21 CFR 820) and therefore applies to the manufacture of both drug products and medical devices.[8, 12] In current study, samples from Batch # 1, 2 and 3 were tested for critical process parameters. Table 1 depicts the results for individual batches. Control variables for purified water were decided based upon its description given in the USP. [13] The water quality was checked for its compliance with USP specifications or not. Conductivity of purified water was measured using conductivity meter at 25^0C.[14] All the specifications of the remaining parameters were set based on pilot study in the R&D department of Herbion Private Limited. Syrup was filled in the washed pet bottle through automated four head filling line. One of the most practical forms of process validation, mainly for non-sterile products, is the final testing of the product to the extent greater than that required in routine quality control.[15] Filled volume was checked to ensure accurate quantity of syrup being filled in the bottle using filling machine. The cap was sealed on automated four head sealing machine and sealing was checked periodically for integrity. The results of filling and sealing evaluation are illustrated in Table 2.

Table 1: Details of critical process parameters for Batch # 1, 2 & 3

TEST PARAMETERS	SPECIFICATIONS	Batch # 1	Batch # 2	Batch # 3
Quality of purified water				
Description	It should be clear colorless liquid, odorless and tasteless.	Comply	Comply	Comply
pH	5.00-7.00	6.75	6.53	6.61
Conductivity (25^0C):	1.0-1.5 µs/cm	1.4 µs/cm	1.3 µs/cm	1.1 µs/cm
Temperature	Should not exceed 80° C	65^0 C	63^0 C	65^0 C
Stirrer speed	2000-3000 rpm	2000rpm	3000rpm	2500rpm
Final mixing Time	50-60 mins.	50 mins.	60 mins.	54 mins.
Clarity of final batch	Must be clear	Clear Liquid	Clear Liquid	Clear Liquid
Quality of syrup				
Description	Brown color syrup	Comply	Comply	Comply
Density	From 1.25 to 1.35 g/ml	1.297 g/ml	1.328 g/ml	1.282 g/ml
pH	From 3.0 to 6.0	3.7	3.8	3.5
Viscosity	100-200poise	161poise	170poise	175poise
Taste	Characteristic sweet taste	Comply	Comply	Comply
Odor	Characteristic	Comply	Comply	Comply

Table 2: Details of filling volume and sealing quality

Batch # 1		Batch # 2		Batch # 3	
Fill Volume	**Sealing Quantity**	**Fill Volume**	**Sealing Quantity**	**Fill Volume**	**Sealing Quantity**
90 ml	Comply	90 ml	Comply	90 ml	Comply
90 ml	Comply	90 ml	Comply	90 ml	Comply
90 ml	Comply	90 ml	Comply	90 ml	Comply
90 ml	Comply	90ml	Comply	90 ml	Comply
90 ml	Comply	90 ml	Comply	90 ml	Comply

CONCLUSION

Pharmaceutical validation and process control provide a certain assurance of batch uniformity and integrity of the product manufactured. The manufacturing process of polyherbal Entoban syrup was found to be reproducible for three batches and all parameters were complying with the specifications and validated as per the guidelines mentioned in prospective process validation.

REFERENCES

1. Bala K, Saini S. Pharma Science Monitor.
2. Jatto E, Okhamafe AO. An Overview of Pharmaceutical Validation and Process Controls in Drug Development. Tropical Journal of Pharmaceutical Research., 2002; 1(2): 115-xx.
3. Food, Administration D. Guide to Inspection of Oral Solid Dosage Forms: Pre/Post Approval Issues for Development and Validation. Rockville, MD: Office of Compliance, Center for Drugs and Biologics., Jan. 1994; 1994.
4. Verma V, Nautiyal U, Kumar MS, Kant C. Process Validation Of Tablets: An Overview.
5. Lavanya G, Sunil M, Eswarudu M, Eswaraiah MC, Harisudha K, Spandana BN. Analytical Method Validation: An Updated Review. International Journal of Pharmaceutical Sciences & Research., 2013; 4(4).
6. Tangri P, Rawat PS. Validation: A Critical Parameter for Quality Control of Pharmaceuticals. Journal of Drug Delivery and Therapeutics., 2012; 2(3).
7. Gaganpreet K, Rana A, Nimrata S, Rajni B. International Research Journal Of Pharmacy.
8. Kant C, Nautiyal U, Kumar MS, Verma V, Singh R. Process Validation: An Overview.
9. Kaur H, Singh G, Seth N. Pharmaceutical Process Validation: A Review. Journal of Drug Delivery and Therapeutics., 2013; 3(4): 189-94.
10. Pérez JR. Quality Risk Management in the FDA-Regulated Industry: ASQ Quality Press; 2012.

11. Ahir KB, Singh KD, Yadav SP, Patel HS, Poyahari CB. Overview of Validation and Basic Concepts of Process Validation. Scholars Academic Journal of Pharmacy., 2014; 3: 178-90.
12. Marinelli A, Verghese G, Yang H, Moldenhauer J, Zec J, Schmitt S. Validation Dictionary 2nd Edition| IVT.
13. Gsell GV. Apparatus for producing USP or WFI purified water. Google Patents, 2004.
14. Desai L, Oza J, Khatri K. Prospective process validation of polyherbal cough syrup formulation. Journal of Advanced Pharmacy Education & Research Oct-Dec., 2012; 2(4).
15. Parida RK. Overview of Pharmaceutical Validation and Process Controls in Drug Development. Pelagia Research Library., 2010; 1(1): 11-9.